Systematic review of economic analyses of health care-associated infections

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Background: Economic evidence is needed to assess the burden of health care-associated infections (HAIs) and cost-effectiveness of interventions aimed at reducing related morbidity and mortality. The objective of this study was conducted to assess the quality of economic evaluations related to HAI and synthesize the evidence.
Methods: A systematic review of research published between January 2001 and June 2004 was conducted. Quality of the publication was estimated using a Likert-type scale. All cost estimates were standardized into a common currency. Descriptive statistics and a logistic regression were conducted to identify predictors of high quality.
Results: 70 studies were audited. There was wide variation in these cost estimates. Publications estimating the cost attributable to an infection were almost 7 times more likely judged to be of higher quality than studies of the cost of interventions ($P < .05$). Papers in which the authors stated the perspective (hospital or societal) were twice as likely to be judged as being of high quality ($P < .05$).
Conclusion: There are more publications and growing interest in estimating the costs of HAI. However, the methods employed vary. We recommend (1) the use of guidelines for authors and editors on conducting an economic analysis, (2) development of more sophisticated mathematical models, and (3) training of infection control professionals in economic methods. (Am J Infect Control 2005;33:501-9.)

Health care-associated infections (HAI) are one of the most serious patient safety issues in health care today. In the United States, the incidence of HAI has been estimated to be approximately 2 million cases annually.[1,2] More than 500,000 of these infections occur in intensive care units (ICUs), and most are associated with the presence of an invasive device such as a central venous catheter or ventilator. The rate of HAI per 1000 patient days increased 36% from 1975 to 1995.[3] Furthermore, it has been estimated that there are approximately 90,000 deaths attributed to HAI annually, ranking it as the fifth leading cause of death in acute care hospitals.[4] These trends suggest that many challenges still exist in the prevention and control of HAI in the health care setting.

The total annual hospital-related financial burden of HAI in the United States was estimated to exceed $4.5 billion in 1992 (using the Consumer Price Inflator, this converts to 6.5 billion in 2004 dollars).[1] However, we found no further national estimates of the burden, and this estimate is based on infection rates measured in the Study on the Efficacy of Nosocomial Infection Control (SENIC) study, which was conducted in the mid-1970s.[5] Hence, these estimates are dated and likely to underestimate the current costs.

Increasingly, there are calls for the application of cost-effective technologies to decrease the burden of illness related to infectious diseases and specifically HAI.[6,7] Therefore, it is critically important to understand both the economic burden of HAI as well as the evidence from cost-effectiveness research examining health-related technologies, services, and programs aimed at reducing HAI disease-related morbidity and mortality. To understand the economic burden of HAI, the resources and related costs of interest are the incremental costs that may be directly attributable to the infection and not the underlying admitting diagnosis. In a previous survey,[8] we audited a decade of published economic evidence on the attributable costs of HAI and interventions aimed at reducing this burden. In that study, we found a wide variation in the cost estimates (eg, $3500 to $40,000 per survivor of bloodstream infection [BSI], in 2000 dollars).[8] Differences in methods used to estimate costs, which has been a chronic problem found in economic evaluations, contributes to the wide range of costs reported.[9-12] In addition, results cited above include estimates of hospital costs only, not costs to the broader health care sector or to society. The objectives of our current study were to update that review and assess the quality of these analyses.

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METHODS

A systematic review of existing published evidence was conducted. Articles were included if they were published between January 2001 and June 2004, had an abstract for review, contained an original cost estimate, and were written in English. To find the published analyses, searches were conducted in MEDLINE, EconoLit, and HealthSTAR using the medical subject headings (MeSH) or text keywords ''nosocomial infections,'' ''infection control,'' or ''hospital acquired infections'' cross referenced with ''costs,'' ''cost analysis,'' ''economics,'' or ''cost-effectiveness analysis.'' In addition, review articles were examined for published articles that met the inclusion criteria, and other published articles that were known to the authors were included. Methodologic articles and editorials were excluded.

Our original audit form containing 23 data elements was based on work from the Harvard Cost-Effectiveness Analysis Registry research team.[13] We piloted and refined the form as needed. Data elements extracted included the type of study (simple cost analysis of HAI or economic evaluation of an intervention to prevent or reduce HAI), source of funding, country of study, type of HAI analyzed, and definition of HAI used (ie, Centers for Disease Control and Prevention [CDC] definition, other definition, or not stated) and whether the study included consideration of antibiotic resistance. Study design elements such as types of costs included, source of cost data, and source of effectiveness data or attributable costs (if applicable) were noted. If the study was an economic evaluation of an intervention, the type of economic evaluation (eg, simple cost analysis without comparison or cost-effectiveness analysis) was categorized. We also noted whether decision analytic models to estimate cost-effectiveness were used.

In accordance with methods recommended to audit systematically the economic evaluations,[14] 2 trained readers audited each study and met for consensus discussions. If there was uncertainty or disagreement on any data element, a third expert reader was consulted. Similar to the Harvard Cost-Effectiveness Analysis registry audit, quality of the analysis was rated on a 7-point Likert scale, with the highest quality scored as 7 and the lowest quality assigned a 1. The quality score assigned to the analysis was based on the mean between the 2 readers. We then dichotomized this variable based on the distribution of data; studies with a mean score of 4 or less were considered low quality and greater than 4 were considered high quality.

Economic (ie, monetary) results were standardized into a common currency and year. When authors stated the year of currency in which their results were reported, we used that year for calculations. If the year was not stated, 2 years prior to publication was used as an estimate of the probable year. All cost estimates were standardized into US currency with use of the Economic Research Federal Reserve Bank of St. Louis/FRED II (http://research.stlouisfed.org/fred2/categories/15) rates for January 1 of the estimated year of the study. In addition, all US dollars were standardized into 2002 values using the Bureau of Labor Statistics Consumer Price Index calculator (http://data.bls.gov/cgi-bin/cpicalc.pl).

Data were entered into an ACCESS Microsoft office database and analyzed using SPSS 11.5 (SPSS Inc, Chicago, IL). Descriptive statistics were computed. A logistic regression was conducted in which the quality of the analysis (high = a mean consensus score of greater than 4, and low = a mean consensus score of 4 or less) was the dependent variable and predictor variables included paper type (cost of infection or cost of intervention), country of study (United States or other), consideration of antibiotic resistance (yes or no), HAI definition (stated, not stated), perspective (stated, not stated), and source of funding (stated, not stated).

To summarize the results of studies, we grouped analyses by type of infection studied (urinary tract infections, ventilator associated pneumonias, BSI, surgical infections, and other). In this synthesis, results were only included if they were originally reported as cost per patient infection or if it was possible to convert the results to this standard outcome.

RESULTS

One hundred fifty-two manuscripts were obtained for review. Of these, 70 studies met our eligibility criteria. See Appendix A for full list of the eligible articles. Table 1 summarizes publications in terms of country of study, funding source, description of HAI analyzed, and economic methods employed.

The majority of the analyses were conducted in the United States. Although the most commonly reported funding source for these studies was government or industry, many authors did not report whether there was or was not a funder. Surgical infections were most commonly analyzed, followed by BSI. Many studies examined organism-specific infections such as vancomycin-resistant enterocci or *Clostridum difficile*.

The most common analytic method was a simple cost analysis of infection, and the majority of the analyses were conducted from the perspective of the hospital. Costs related to outpatient or nonhealth care services were generally not included. Actual microcosting (eg, time and motion studies and/or costs of specific items) was the most frequent source of cost estimation.

Table 1. Cost analyses related to HAI January 2001 to June 2004

Paper characteristic	n	%	Economic methods	n	%
Country of study			Type of analysis		
United States	39	56	Cost analysis of infection	40	57
Europe	17	24	Cost analysis of intervention†	30	43
Australia/New Zealand	4	6			
Other	10	14	Perspective of analysis		
			Hospital	63	90
Source of funding*			Health care sector	6	9
Government	14	20	Societal	1	1
Industry	13	19			
Foundation	2	3	Costs included*		
In-kind	1	1	Intervention	25	36
Not stated	43	61	Hospitalization	60	86
			Outpatient	3	4
HAI analyzed			Antibiotics	9	13
Surgical	18	23.7	Nonhealth care	0	0
Bloodstream	14	18.4			
Pneumonia	6	7.9	Source of cost estimate*		
Urinary tract	2	2.6	Published data	14	20
Organism specific	25	32.9	Microcosting	50	71
Other	11	14.5	Estimated by authors	29	41
			Claims	25	36
Antibiotic resistance considered			Other	3	4
Yes	21	30			
			Time horizon		
Definition of HAI			1 year or less	69	99
CDC	29	41	Greater than 1 year	1	1
Other	31	44			
Not stated	10	14	Quality score		
			4 or less	35	50
			Greater than 4	35	50

N = 70.
*Categories are not mutually exclusive.
†Twenty of these studies had no comparator and therefore were not formal economic evaluations. Five of the studies were cost-effectiveness analyses, 3 were cost-consequence analyses, and 2 were cost-minimization analyses.

Table 2. Predictors of high-quality studies*

	Odds ratio	95% CI
NI definition stated	7.6	0.1-4.5
Cost analysis of infection compared with cost analysis of intervention	6.5†	1.8-23.4
Perspective stated	2.3†	1.1-4.8
United States compared with other countries	3.0	0.8-11.1
Antibiotic resistance	1.7	0.4-6.3
Funding source stated	1.2	0.6-2.2

*High quality defined as a quality score greater than 4 out of a range from 1 to 7.
†$P < .05$.

The results of the logistic regression are displayed in Table 2. The type of paper was a significant predictor of study quality, with publications estimating the cost attributable to an infection almost 7 times more likely judged to be higher quality than studies of the cost of interventions. Papers in which the authors stated the perspective (hospital or societal) were twice as likely to be judged high quality.

Forty-five simple cost analyses could be standardized into cost per patient infections, for a total of 47 separate results. Twenty-four of these studies examined a specific type of infection: surgical site, BSI, ventilator-associated pneumonia, and urinary tract infections. On average, BSIs were found to be the most expensive (Table 3); however, the standard deviations of all infection types were quite large, indicating wide variations in the estimated costs per patient.

DISCUSSION

We have found substantial growth in published evidence estimating the cost of HAI and interventions aimed at decreasing the related morbidity and mortality. In our previous audit using the same inclusion criteria, there were only 55 eligible articles found over a 10-year period compared with the 70 publications we found over a two-and-half-year period.[8] However, as in the previous audit, the majority of the articles were simple cost analyses conducted from the hospital rather than the societal perspective, and the methods used in these analyses were varied. As in our previous audit, BSIs were the most expensive with comparable wide variation in the estimated costs.

Over a two-and-a-half-year period, we found substantial growth in published evidence estimating the cost of HAI and interventions aimed at decreasing related morbidity and mortality. This growth may be related to the overall growth in publications, or it may reflect an increased interest to understand financial implications of HAI as well as increased pressure to demonstrate the cost-effectiveness of infection control departments. However, because of lack of standard methods, caution is needed when interpreting this growing body of evidence.

There has been a number of efforts to standardize the conduct and reporting of economic evaluations of health care technology.[15-18] The Panel on Cost-Effectiveness Analysis in Health Care and Medicine convened by the US Public Health Service Department suggested a standard set of methodologic practices intended to improve the comparability of cost-effectiveness evidence, which is called a *Reference Case*.[15-18] Some of the recommendations for an ideal reference case include adopting a societal perspective, reporting results in terms of dollars per quality adjusted life year (QALY) gained (called a cost-utility analysis), including downstream net costs (and savings), discounting future

Table 3. Attributable costs of HAI

	Attributable costs		Range		
Infection type	**Mean**	**SD**	**Minimum**	**Maximum**	**References**
Surgical site infection	25,546	39,875	1783	134,602	30-37
Bloodstream infection	36,441	37,078	1822	107,156	38-46
Ventilator-associated pneumonia	9969	2920	7904	12,034	47,48
Urinary tract infection	1006	503	650	1361	49,50

Only articles that could be summarized using the outcome cost per patient were used in this analysis.

costs and QALYs, and conducting a minimal standard set of sensitivity analyses (ie, analyses in which a parameter is varied to estimate the degree of influence it has on the results of the base analysis). In addition, the panel developed a checklist to be used for journal reports (Table 4).

Unfortunately, the analyses we audited were for the most part much less sophisticated and did not meet these recommended standards. Many of the studies only reported aggregate estimates of costs and could not be included in our synthesis (Table 3). Although the recommendations in Table 4 are more rigorous, at the very least, analysts should provide data and/or calculate costs per person to have a standard outcome across studies. Of note, economic analyses regarding infection control interventions should further consider externalities such as the impact on herd effects and herd immunity of communicable infectious disease interventions to prevent distortion of cost-effectiveness estimates.[19]

Other previous auditors of economic literature have also raised concerns about the quality of the published analyses.[10-12,20] There is some evidence that the quality is improving,[13] but improvement is clearly still needed in the cost studies related to HAI. Although the results of the individual analyses audited have potential implications for clinical decision making, guideline development, and resource allocation, the quality of these analyses should be improved if they are to have a wide impact on health policy.

There are several approaches that could be used to improve the quality of economic analyses. First, journal editors could adopt guidelines for reviewing economic studies. The *British Medical Journal* has developed such a guideline.[21,22] The guidelines are grouped into 10 sections under 3 headings: study design, data collection, and analysis and interpretation of results. Under each section is a commentary outlining the reasons for the requirements and the main unresolved methodologic issues and explaining why firm guidelines cannot be given in some cases. The guidelines are similar to the recommendations in

Table 4. Checklist for Journal Report of Economic Evaluation

1. Framework
   - Background of the problem
   - General framing and design of the problem
   - Target population for the intervention
   - Other program descriptors
   - Description of comparator programs
   - Boundaries of the analysis
   - Time horizon
   - Statement of the perspective of the analysis
2. Data and methods
   - Description of event pathway
   - Identification of outcomes of interest in the analysis
   - Description of model used
   - Modeling assumptions
   - Diagram of event pathway/model
   - Software used
   - Complete information about the sources of effectiveness data, cost data, and preference weights
   - Methods for obtaining estimates of effectiveness, costs, and preferences
   - Critique of data quality
   - Statement of year costs
   - Statement of method used to adjust costs for inflation
   - Statement of type of currency
   - Sources and methods for obtaining expert judgment
   - Statement of discount rates
3. Results
   - Results of model validation
   - Base results (discounted and undiscounted): total costs and effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios
   - Results of sensitivity analyses
   - Other estimates of uncertainty, if available
   - Graphical representation of results
   - Aggregate cost and effectiveness information
   - Disaggregated results, as relevant
   - Secondary analyses using 5% discount rate
4. Discussion
   - Summary of reference case results
   - Summary of sensitivity analysis assumptions having important ethical implications
   - Limitations of the study
   - Relevance of the study results for specific policy questions or decisions
   - Results of related economic evaluations
5. Technical report in appendix or available on request

Adapted from Gold et al.[16]

Table 4. Editors could also develop a cadre of reviewers experienced in economic evaluation.

Second, we recommend continued development of sophisticated mathematical policy models. Mathematical models are used routinely to guide public policy decisions in many areas that affect human life and health. Environmental regulation and military planning and strategy are 2 areas in which models have gained stature as policy tools.[23-25] Models are also routinely used in economic forecasting with implications for macroeconomic policy, in transportation planning with implications for the location and operation of traffic controls and the design of roadways, and in many other areas.[26]

The US government has a long history of using and developing models to guide public health policy. Models rather than direct evidence have been used to support vaccine recommendations by the CDC at least since the late 1960s. The CDC's report ''An Ounce of Prevention'' reviewed and endorsed a variety of model-based estimates of gains in quality-adjusted life expectancy and cost-effectiveness ratios.[27] The Institute of Medicine has twice issued recommendations to use models to recommend priorities for the development of new vaccines.[28,29]

The development of mathematical models to assess cost-effectiveness of interventions requires specific expertise. In the summer of 2004, in an effort to help nurse researchers better understand these techniques, a 2-day workshop was held by the National Institute of Nursing Research. Expert faculty from the Agency for Healthcare Research and Quality (AHRQ), Johns Hopkins University, and Columbia University provided a series of lectures and breakout sessions to help the nurse researcher understand the mechanics of these types of models (http://www.ijhn.jhmi.edu/CostEffectivenessAnalysis/overview.htm). Developing such workshops for infection control professionals may increase the rigor of the economic evaluations found in this literature.

In summary, there is increased interest in the economic evidence regarding the attributable costs of HAI and the cost-effectiveness of interventions aimed at reducing the morbidity and mortality associated with HAI. This has resulted in a growing number of publications. Surgical and BSI are the most frequently studied infections and the most expensive. However, there is wide variation in the methods used, limiting the impact of these analyses. The quality of economic evaluations should be increased to inform better the decision makers and clinicians.

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Appendix A. Studies audited

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